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Mikhail Bayley

(TYPED OR PRINTED NAME OF PERSON MAILING PAPER)

Mikhail Bayley

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APPLICATION

for

UNITED STATES LETTERS PATENT

on

PROTECTED FORMS OF PHARMACOLOGICALLY ACTIVE AGENTS AND USES THEREFOR

by

Tingmin Wang and Ching-San Lai

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Attorneys

Gray Cary Ware & Freidenrich
4365 Executive Drive, Suite 1600
San Diego, California 92121-2189

Protected Forms of Pharmacologically Active Agents and Uses Therefor

FIELD OF THE INVENTION

The present invention relates to novel forms of pharmacologically active agents, and methods for the preparation and use thereof. In a particular aspect of the invention, methods are provided for treating pathological conditions with a protected form of one or more pharmacologically active agents, thereby reducing the occurrence of side-effects caused thereby.

BACKGROUND OF THE INVENTION

Despite the advent of modern pharmaceutical technology, many drugs still possess untoward toxicities which often limit the therapeutic potential thereof. For example, although non-steroid anti-inflammatory drugs (NSAIDs) are a class of compounds which are widely used for the treatment of inflammation, pain and fever, NSAIDs (e.g., naproxen, aspirin, ibuprofen and ketoprofen) can cause gastrointestinal ulcers, a side-effect that remains the major limitation to the use of NSAIDs (see, for example, J. L. Wallace, in Gastroenterol. 112:1000-1016 (1997); A. H. Soll et al., in Ann Intern Med. 114:307-319 (1991); and J. Bjarnason et al., in Gastroenterol. 104:1832-1847 (1993)).

There are two major ulcerogenic effects of NSAIDs: (1) irritant effects on the epithelium of the gastrointestinal tract and (2) suppression of gastrointestinal prostaglandin synthesis. In recent years, numerous strategies have been attempted to design and develop new NSAIDs that reduce the damage to the gastrointestinal tract. These efforts, however, have largely been unsuccessful. For example, enteric coating or slow-release formulations designed to reduce the topical irritant properties of NSAIDs have been shown to be ineffective in terms of reducing the incidence of clinically significant side effects, including perforation and bleeding (see, for example, D. Y.

Graham et al., in Clin. Pharmacol. Ther. 38:65-70 (1985); and J. L. Carson, et al., in Arch. Intern. Med., 147:1054-1059 (1987)).

It is well recognized that aspirin and other NSAIDs exert their pharmacological effects through the non-selective inhibition of cyclooxygenase (COX) enzymes, thereby blocking prostaglandin synthesis (see, for example, J. R. Van in Nature, 231:232-235 (1971)). There are two types of COX enzymes, namely COX-1 and COX-2. COX-1 is expressed constitutively in many tissues, including the stomach, kidney, and platelets, whereas COX-2 is expressed only at the site of inflammation (see, for example, S. Kargan et al. in Gastroenterol., 111:445-454 (1996)). The prostagladins derived from COX-1 are responsible for many of the physiological effects, including maintenance of gastric mucosal integrity.

Many attempts have been made to develop NSAIDs that only inhibit COX-2, without impacting the activity of COX-1 (see, for example, J.A. Mitchell et al., in Proc. Natl. Acad. Sci. USA 90:11693-11697 (1993); and E.A. Meade et al., in J. Biol. Chem., 268:6610-6614 (1993)). There are several NSAIDs presently on the market (e.g., rofecoxib and celecoxib) that show marked selectivity for COX-2 (see, for example, E. A. Meade, supra.; K. Glaser et al., in Eur. J. Pharmacol. 281:107-111 (1995) and Kaplan-Machlis, B., and Klostermeyer, BS in Ann Pharmacother. 33:979-88, (1999)). These drugs appear to have reduced gastrointestinal toxicity relative to other NSAIDs on the market.

On the basis of encouraging clinical as well as experimental data, the development of highly selective COX-2 inhibitors appears to be a sound strategy to develop a new generation of anti-inflammatory drugs. However, the physiological functions of COX-1 and COX-2 are not always well defined. Thus, there is a possibility that prostagladins produced as a result of COX-1 expression may also contribute to inflammation, pain and fever. On the other hand, prostagladins produced by COX-2 have been shown to play important physiological functions, including the initiation and maintenance of labor and in the regulation of bone resorption (see, for example, D. M.

Slater et al., in Am. J. Obstet. Gynecol., 172:77-82 (1995); and Y. Onoe et al., in J. Immunol. 156:758-764 (1996)), thus inhibition of this pathway may not always be beneficial. Considering these points, highly selective COX-2 inhibitors may produce additional side effects above and beyond those observed with standard NSAIDs, therefore such inhibitors may not be highly desirable.

Accordingly, there is still a need in the art for modified forms of NSAIDs which cause a reduced incidence of side-effects, relative to the incidence of side-effects caused by such pharmacologically active agents in unmodified form.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a new class of modified NSAIDs which cause a much lower incidence of side-effects than are typically observed with unmodified NSAIDs due to the protective effects imparted by modifying the NSAIDs as described herein.

There are a number of advantages provided by modified NSAIDs according to the invention including:

(i) reduced irritant effects (e.g., contact irritation) of NSAIDs, and

(ii) enhanced tissue delivery of the drug as a result of a decrease in net charges on the molecule, particularly for acidic NSAIDs such as naproxen, aspirin, diclofenac and ibuprofen, thereby reducing the quantity of material which must be delivered to achieve an effective dosage.

In accordance with the present invention, cleavage of the modified NSAIDs described herein from the modified group appended thereto releases the pharmaceutically active agent.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the total length of intestinal ulcers measured after three daily doses of NSAID in unfasted male Sprague-Dawley rats (150-200 g) treated with vehicle, naproxen or equimolar invention composition (compound 19). * $P < 0.05$ by unpaired t-test.

Figure 2 illustrates the total length of intestinal ulcers measured after 14 daily doses of NSAID in unfasted male Sprague-Dawley rats (150-200 g) treated with vehicle (bar 7), three doses of naproxen (bar 1: 50 mg/kg, bar 2: 45 mg/kg, bar 3: 40 mg/kg), or three equimolar doses of invention composition (compound 19) (bars 4-6). * $P < 0.05$ by unpaired t-test vs. corresponding dose of naproxen.

Figure 3 illustrates the inhibition of paw volume increases in the uninjected feet of Lewis male rats in which arthritis was induced by intradermal injection of adjuvant into the footpad. Rats were injected on day 0 and treated once daily from days 8 to 15 with vehicle, naproxen (10 mg/kg), or invention composition (compound 19) at equivalent dose. Paw volumes were measured with a Plethysmometer on days 5 and 15. Closed circles = naproxen; squares = invention composition.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided compounds comprising a modified NSAID, wherein the NSAID is covalently attached either directly or through a linker molecule to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety. Invention compounds have the structure:

X-L-Z

wherein:

X = a non-steroidal anti-inflammatory drug (NSAID),

L = an optional linker/spacer, and

Z = a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

NSAIDs contemplated for modification in accordance with the present invention include acetaminophen (Tylenol, Datril, etc.), aspirin, ibuprofen (Motrin, Advil, Rufen, others), choline magnesium salicylate (Triasate), choline salicylate (Anthropan), diclofenac (voltaren, cataflam), diflunisal (dolobid), etodolac (lodine), fenoprofen calcium (nalfon), flurbiprofen (ansaid), indomethacin (indocin, indometh, others), ketoprofen (orudis, oruvail), carprofen, indoprofen, ketorolac tromethamine (toradol), magnesium salicylate (Doan's, magan, mobidin, others), meclofenamate sodium (meclomen), mefenamic acid (relafan), oxaprozin (daypro), piroxicam (feldene), sodium salicylate, sulindac (clinoril), tolmetin (tolectin), meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, indoprofen, remifenzone, salsalate, tiaprofenic acid, flosulide, and the like. Presently preferred NSAIDs employed in the practice of the invention include naproxen, aspirin, ibuprofen, flurbiprofen, indomethacin, ketoprofen, carprofen, and the like.

Invention compounds can be readily prepared in a variety of ways either by direct reaction of NSAIDs with the sulfur-containing functional group or indirectly through a suitable linker molecule.

The components of invention compositions are directly or indirectly covalently attached employing a variety of linkages (including an optional linker), e.g., ester linkages, disulfide linkages, amide linkages, immine linkages, enamine linkages, ether linkages, thioether linkages, imide linkages, sulfate ester linkages, sulfonate ester linkages, sulfone linkages, sulfonamide linkages, phosphate ester linkages, carbonate linkages, O-glycosidic linkages, S-glycosidic linkages, and the like. Such linkages can

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be accomplished using standard synthetic techniques as are well known by those of skill in the art, either by direct reaction of the starting materials, or by incorporating a suitable functional group on the starting material, followed by coupling of the reactants.

When the pharmacologically active agents contemplated for use herein contain suitable functionality thereon, e.g., hydroxy, amino, carboxy, and the like, invention modified NSAIDs can be prepared by direct linkage between the two agents. Alternatively, the NSAIDs can be functionalized so as to facilitate linkage between the two agents. When present, linker/spacer L has the following structure:

-W-R-

wherein:

R is optional, and when present is alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, heterocyclic, substituted heterocyclic, oxyalkylene, substituted oxyalkylene, alkenylene, substituted alkenylene, arylene, substituted arylene, alkarylene, substituted alkarylene, aralkylene or substituted aralkylene, and

W is ester, reverse ester, thioester, reverse thioester, amide, reverse amide, phosphate, phosphonate, imine, enamine, or the like.

Functional groups contemplated by the present invention are sulfur-based. Examples of suitable sulfur-containing functional groups include sulfonate, reverse sulfonate, sulfonamide, reverse sulfonamide, sulfone, sulfinate, reverse sulfinate, and the like. In a particular aspect of the invention, the sulfur-based moiety is sulfonate or reverse sulfonate. In a particularly preferred aspect of the invention, the sulfonate is an optionally substituted aromatic sulfonate such as tosylate or brosylate.

Other preferred sulfur-based functional groups contemplated by the present invention include sulfones. Preferably, the sulfone is an optionally substituted alkyl or aromatic sulfone.

In one aspect of the invention, Z may have the following structure:

$$-Y-S(O)_n-Y'-Q$$

wherein:

each of Y and Y' are optionally present, and when present are independantly –O- or –NR'-, wherein R' is H or an optionally substituted hydrocarbyl moiety;

n is 1 or 2, and

Q is H or an optionally substituted hydrocarbyl moiety.

As employed herein, "hydrocarbyl" embraces alkyl, substituted alkyl, oxyalkyl, substituted oxyalkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, monocyclic heterocylic, substituted monocyclic heterocyclic, monocyclic aromatic, monosubstituted monocyclic aromatic, or the like.

As employed herein, "alkyl" refers to hydrocarbyl radicals having 1 up to 20 carbon atoms, preferably 2-10 carbon atoms; and "substituted alkyl" comprises alkyl groups further bearing one or more substituents selected from hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, halogen, trifluoromethyl, cyano, nitro, nitrone, amino, amido, -C(O)H, acyl, oxyacyl, carboxyl, carbamate, sulfonyl, sulfonamide, sulfuryl, and the like.

As employed herein, "oxyalkyl" refers to the moiety –O-alkyl-, wherein alkyl is as defined above, and "substituted oxyalkyl" refers to oxyalkyl groups further bearing one or more substituents as set forth above.

As employed herein, "cycloalkyl" refers to cyclic ring-containing groups containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl groups further bearing one or more substituents as set forth above.

As employed herein, "heterocyclic" refers to cyclic (i.e., ring-containing) groups containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heterocyclic" refers to heterocyclic groups further bearing one or more substituents as set forth above.

As employed herein, "alkenyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkenyl" refers to alkenyl groups further bearing one or more substituents as set forth above.

As employed herein, "alkynyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkynyl" refers to alkynylene groups further bearing one or more substituents as set forth above.

As employed herein, "monocyclic aromatic" refers to aromatic groups having in the range of 5 up to 7 carbon atoms and "monosubstituted monocyclic aromatic" refers to aromatic groups further bearing one of the substituents set forth above.

As employed herein, “alkylene” refers to divalent hydrocarbyl radicals having 1 up to 20 carbon atoms, preferably 2-10 carbon atoms; and "substituted alkylene" comprises alkylene groups further bearing one or more substituents as set forth above.

As employed herein, "cycloalkylene" refers to cyclic ring-containing groups containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkylene" refers to cycloalkylene groups further bearing one or more substituents as set forth above.

As employed herein, “oxyalkylene” refers to the moiety –O-alkylene-, wherein alkylene is as defined above, and “substituted oxyalkylene” refers to oxyalkylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkenylene" refers to divalent, straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkenylene" refers to alkenylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkynylene" refers to divalent straight or branched chain hydrocarbyl groups having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkynylene" refers to alkynylene groups further bearing one or more substituents as set forth above.

As employed herein, "arylene" refers to divalent aromatic groups having in the range of 6 up to 14 carbon atoms and "substituted arylene" refers to arylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkylarylene" refers to alkyl-substituted arylene groups and "substituted alkylarylene" refers to alkylarylene groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkylene" refers to aryl-substituted alkylene groups and "substituted arylalkylene" refers to arylalkylene groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkenylene" refers to aryl-substituted alkenylene groups and "substituted arylalkenylene" refers to arylalkenylene groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkynylene" refers to aryl-substituted alkynylene groups and "substituted arylalkynylene" refers to arylalkynylene groups further bearing one or more substituents as set forth above.

Diseases and conditions contemplated for treatment in accordance with the present invention include inflammatory and infectious diseases, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease), diabetes, arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation (e.g., liver inflammation, renal inflammation, and the like), burn, infection (including bacterial, viral, fungal and parasitic infections), hemodialysis, chronic fatigue syndrome, stroke, cancers (e.g., breast, melanoma, carcinoma, and the like), cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors (e.g., neuroblastoma), malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, hepatitis, renal failure, liver disease (e.g., chronic hepatitis C), drug-induced lung injury (e.g., paraquat), myasthenia gravis (MG), ophthalmic diseases, post-angioplasty, restenosis, angina, coronary artery disease, and the like.

In accordance with another embodiment of the present invention, there are provided methods for the preparation of modified NSAIDs, said method comprising covalently attaching a NSAID to a sulfur-containing functional group containing an

optionally substituted hydrocarbyl moiety. The resulting compound provides a latent form of the pharmacologically active agent, releasing the biological activity thereof only when the compound is cleaved (e.g., by an esterase, amidase or other suitable enzyme).

As readily recognized by those of skill in the art, invention compounds can be prepared in a variety of ways. See, for example, Scheme 1, wherein NSAID, **X**, bearing a carboxylic moiety can be reacted either directly with the sulfur-containing functional group (Scheme 1a) or indirectly through a linker molecule (Scheme 1b).

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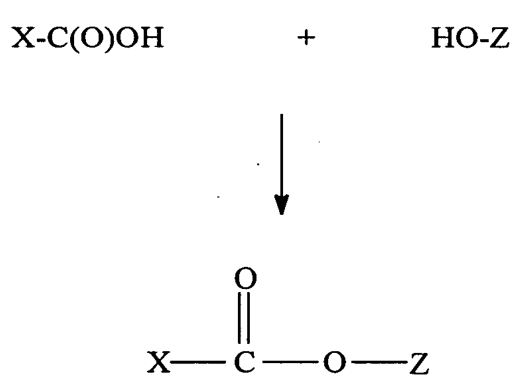
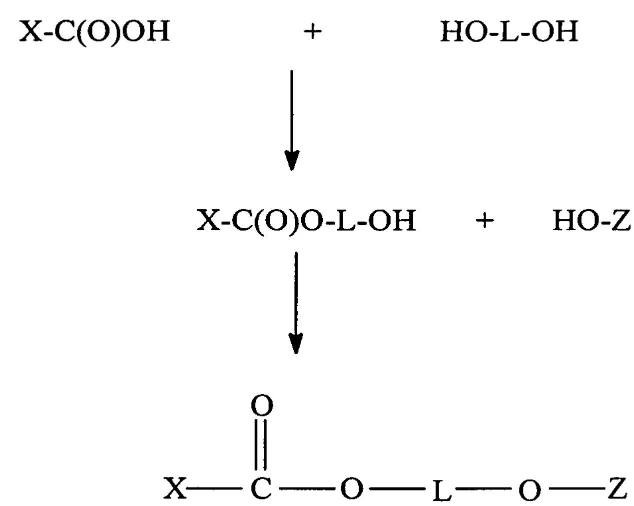
Scheme 1a



Scheme 1b



Employing these general reaction schemes, invention modified NSAIDs can be prepared from a wide variety of pharmacologically active agents. See, for example, Examples 1-29 provided herein.

In accordance with yet another embodiment of the present invention, there are provided methods for reducing the side effects induced by administration of NSAIDs to a subject, said method comprising covalently attaching a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety to said NSAID prior to administration to said subject.

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In accordance with still another embodiment of the present invention, there are provided methods for enhancing the effectiveness of NSAIDs, said method comprising covalently attaching a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety to said NSAID.

In accordance with a still further embodiment of the present invention, there are provided improved methods for the administration of NSAIDs to a subject for the treatment of a pathological condition, the improvement comprising covalently attaching said NSAID to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety prior to administration thereof to said subject.

Those of skill in the art recognize that the modified NSAIDs described herein can be delivered in a variety of ways, such as, for example, orally, intravenously, subcutaneously, parenterally, rectally, by inhalation, and the like.

Depending on the mode of delivery employed, the modified NSAIDs contemplated for use herein can be delivered in a variety of pharmaceutically acceptable forms. For example, the invention modified NSAIDs can be delivered in the form of a solid, solution, emulsion, dispersion, micelle, liposome, and the like.

Thus, in accordance with still another embodiment of the present invention, there are provided physiologically active composition(s) comprising invention modified NSAIDs in a suitable vehicle rendering said compounds amenable to oral delivery, transdermal delivery, intravenous delivery, intramuscular delivery, topical delivery, nasal delivery, and the like.

Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a micelle, a liposome, and the like, wherein the resulting composition contains one or more of the modified NSAIDs of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. Invention modified

NSAIDs may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. Invention modified NSAIDs are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

Pharmaceutical compositions containing invention modified NSAIDs may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing inventon modified NSAIDs in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874, to form

osmotic therapeutic tablets for controlled release.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the invention modified NSAIDs are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the invention modified NSAIDs are mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Invention modified NSAIDs contemplated for use in the practice of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the invention modified NSAIDs with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

In general, the dosage of invention modified NSAIDs employed as described herein falls in the range of about 0.01 mmoles/kg body weight of the subject/hour up to about 0.5 mmoles/kg/hr. Typical daily doses, in general, lie within the range of from about 10 μg up to about 100 mg per kg body weight, and, preferably within the range of from 50 μg to 10 mg per kg body weight and can be administered up to four times daily. The daily IV dose lies within the range of from about 1 μg to about 100 mg per kg body weight, and, preferably, within the range of from 10 μg to 10 mg per kg body weight.

In accordance with yet another embodiment of the present invention, there are provided improved methods for the treatment of a subject suffering from a pathological condition by administration thereto of a NSAID , the improvement comprising covalently attaching said NSAID to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety prior to administration thereof to said subject.

Thus, invention method for the treatment of a subject afflicted with a pathological condition comprises administering to a subject an effective amount of a modified pharmacologically active agent,

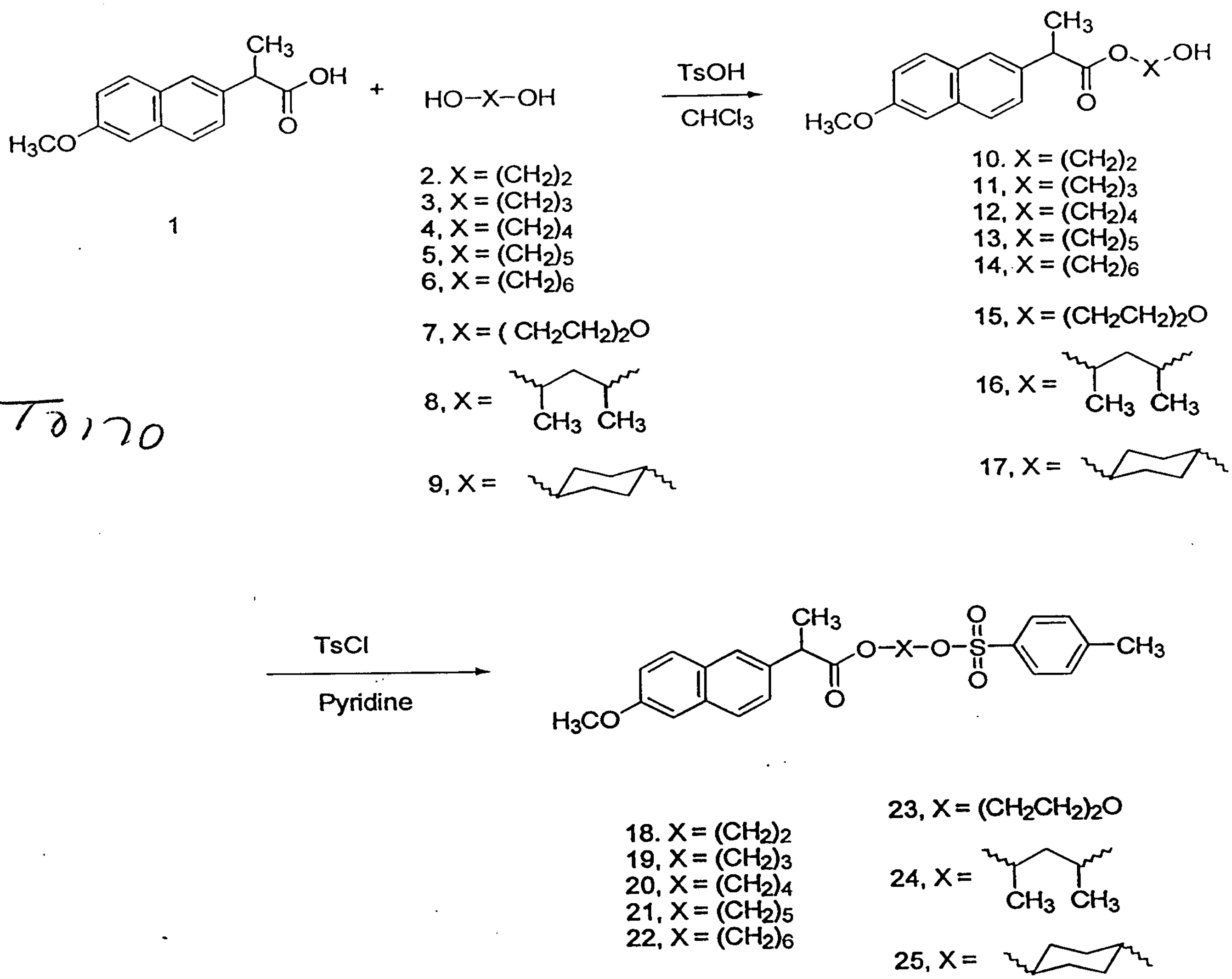
wherein said pharmacologically active agent is a NSAID, and is effective for treatment of said condition, and

wherein said pharmacologically active agent has been modified by the covalent attachment thereto of a sulfur-containingr functional group containing an optionally substituted hydrocarbyl moiety.

The invention will now be described in greater detail by reference to the following non-limiting examples.

The syntheses described in Examples 1-8 are outlined in Scheme 2.

Scheme 2



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Example 1

Compound 10 (Scheme 2). A mixture of Naproxen (**1**) (23 g, 0.1 mol), ethylene glycol (**2**) (27.9 ml, 0.5 mol) and toluenesulfonic acid (TsOH) (1.27g, 6.7 mmol) in $CHCl_3$ was heated to reflux for 4 h. The reaction solution was washed with water, 10% Na_2CO_3 solution and water. The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by crystallization from CH_2Cl_2 and hexanes to give 25.7g (94%) of the compound **10** as a white crystal ; ^{1}H NMR ($CDCl_3$) δ 1.59 (d, 3H), 1.62 (br, 1H, ex D_2O), 3.74 (t, 2H), 3.90 (q, 1H), 3.91 (s, 3H), 4.21 (t, 2H), 7.11 (m, 2H), 7.39 (d, 1H), 7.69 (m, 3H); ^{13}C NMR ($CDCl_3$) d 18.7, 45.6, 55.5, 61.4, 66.6, 105.8, 119.3, 126.1, 126.2, 127.5, 129.1, 129.5, 133.9, 135.7, 157.9, 175.2; MS (ESI) *m/z* 273 (M-1).

Compound 18 (Scheme 2). To a solution of compound **10** (24.5g, 89 mmol) in 100 ml of pyridine was added tosyl chloride (TsCl) (34.1g, 179 mmol). The resulting solution was stirred at 0° C for 2.5h. The reaction solution was then poured into 300 ml of water and then 200 ml of ether was added. The layers were separated and the organic phase was washed with water (300 x 5) and dried (Na_2SO_4). After the solvent was evaporated, the residue was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give 35.1g (92%) of the pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.55(d, 3H), 2.40 (s, 3H), 3.91 (q, 1H), 4.18 (m, 4H), 7.12 (m, 2H), 7.24 (m, 2H), 7.37 (d, 1H), 7.66 (d, 1H), 7.70 (m, 4H); MS (ESI) *m/z* 429 (M+1).

Example 2

Compound 11 (Scheme 2). Compound **11** was prepared as described above for the preparation of compound **10,** this time employing naproxen (**1**) and 1,3-propanediol (**3**). The resulting compound **11** was purified by crystallization from dichloromethane and hexanes with a 92% yield. ^{1}H NMR ($CDCl_3$) δ 1.59 (d, 3H), 1.78 (m, 2H), 1.87 (br, 1H, D_2O ex), 3.53 (t, 2H), 3.87 (q, 1H), 3.91 (s, 3H), 4.23 (t, 2H),

7.11 (d, 1H), 7.15 (m, 1H), 7.41 (q, 1H), 7.66 (d, 1H), 7.69 (s, 1H), 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.6, 31.8, 45.7, 55.5, 59.2, 61.9, 77.0, 77.2, 77.5, 105.8, 119.2, 126.1, 126.3, 127.4, 129.1, 129.4, 133.9, 135.7, 157.8, 175.3; and MS (ESI) *m/z* 289.4 (M+1).

Compound 19 (Scheme 2). Compound **19** was prepared as described above for the preparation of compound **18,** this time employing compound **11** and TsCl. Compound **19** was purified by crystallization from ether and hexane with an yield of 95%; ^{1}H NMR ($CDCl_3$) δ 1.54 (d, 3H), 1.91 (m, 2H), 2.42 (s, 3H), 3.79 (q, 1H), 3.92 (s, 3H), 3.99 (t, 2H), 4.10 (t, 2H), 7.11 d, 1H), 7.15 (q, 1H), 7.26 (d, 2H), 7.34 (d, 2H), 7.62(d, 1H), 7.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 18.5, 21.8, 28.4, 45.5, 55.5, 60.6, 66.9, 105.8, 119.2, 126.0, 126.3, 127.4, 128.0, 129.1, 129.5, 130.1, 133.1, 133.9, 135.6, 145.0, 157.9, 174.5; MS (ESI) *m/z* 421.1 (M-1).

Example 3

Compound 12 (Scheme 2). Compound **12** was prepared as described above for the preparation of compound **10,** this time employing naproxen (**1**) and 1,4-butanediol (**4**). Compound **12** was purified by crystallization from dichloromethane and hexanes with a 90% yield; ^{1}H NMR ($CDCl_3$) δ 1.48 (m, 2H), 1.59 (d, 3H), 1.64 (m, 2H), 1.85 (s, 1H, D_2O, ex), 3.52 (t, 2H), 3.85 (q, 1H), 3.89 (s, 3H), 4.10 (t, 2H), 7.10-7.15 (m, 2H), 7.42 (, d, 1H), 7.66-7.7- (m, 3H); MS (ESI) *m/z* 325.4 (M+ Na).

Compound 20 (Scheme 2). Compound **20** was prepared as described above for the preparation of compound **18,** this time employing compound **12** and TsCl. The compound **20** was purified by crystallization from ether and hexane with an yield of 93%; ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 3H), 1.53-1.62 (m, 4H), 2.43 (s, 3H), 3.82 (q, 1H), 3.92 (s, 3H), 3.94 (m, 2H), 4.02 (m, 2H), 7.11-7.15 (m, 2H), 7.30 (d, 2h), 7.38 (d, 1H), 7.64 (d, 1H), 7.70 (d, 2H), 7.75 (d, 2H); MS (ESI) *m/z* 457.5 (M+1).

Example 4

Compound 13 (Scheme 2). Compound **13** was prepared as described above for the preparation of compound **10,** this time employing naproxen (**1**) and 1,5-pentanediol (**5**). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated under high vaccum to give a quantitative yield of the compound **13**. The compound was used to make compound **21** without further purification; ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 2H), 1.46 (m, 2H), 1.55 (d, 3H), 1.59 (m, 2H), 3.51 (t, 2H), 3.85 (q, 1H), 3.91 (s, 3H), 4.09 (t, 2H), 7.11-7.15 (m, 2H), 7.40 (q, 1H), 7.66-7.70 (m, 3H); MS (ESI) *m/z* 317.5 (M+1).

Compound 21 (Scheme 2). Compound **21** was prepared as described above for the preparation of compound **18,** this time employing compound **13** and TsCl. Compound **21** was purified by crystallization from ether and hexane with a 95% yield; ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 2H), 1.48-1.58 (m, 4H), 1.59 (d, 3H), 2.43 (s, 3H), 3.84 (q, 1H), 3.89 (t, 2H), 3.91 (s, 3H), 4.01 (t, 2H),7.11-7.15 (m, 2H), 7.32 (q, 2H), 7.39 (q, 1H), 7.65 (d, 1H), 7.70 (m, 2H), 7.75 (d, 2H); MS (ESI) *m/z* 471.7 (M+1).

Example 5

Compound 14 (Scheme 2). Compound **14** was prepared as described above for the preparation of compound **10,** this time employing naproxen (**1**) and 1,6-hexanediol (**6**). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound **14** as a solid. The compound was used to make compound **22** without further purification; ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 4H), 1.43 (m 2H), 1.56 (d, 3H), 1.54 (m, 2H), 3.51 (t, 2H), 3.85 (q, 1H), 4.01 (m, 2H), 7.10-7.15 (m 2H), 7.40 (q, 1H), 7.66-7.70 (m, 3H); MS (ESI) *m/z* 331.7 (M+1).

Compound 22 (Scheme 2). Compound **22** was prepared as described above for the preparation of compound **18,** this time employing compound **14** and TsCl. Compound **22** was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give compound **22** as a pale yellow oil; The ^{1}H NMR

($CDCl_3$) δ 1.12 –1.22 (m, 4H), 1.46-1.52 (m, 4H), 1.57 (d, 3H), 2.43 (s, 3H), 3.84 (q, 1H), 3.92 (s, 3H), 3.93 (m, 2H), 4.03 (m, 2H), 7.11-7.77 (m, 10H); MS (ESI) *m/z* 485.6 (M+1).

Example 6

Compound 15 (Scheme 2). Compound **15** was prepared as described above for the preparation of compound **10,** this time employing naproxen (**1**) and di(ethylene glycol) (**7**). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound **15**. The compound was used to make compound **23** without further purification; ^{1}H NMR ($CDCl_3$) d 1.58 (d, 3H), 1.93 (br, 1H, D_2O ex), 3.43 (t, 2H), 3.59 (t, 2H), 3.62 (t, 2H), 3.89 (q, 1H), 3.90 (s, 3H), 4.25 (m, 2H), 7.11-7.15 (m, 2H), 7.40-7.42 (m, 1H), 7.70 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 18.7, 45.6, 55.5, 61.8, 64.0, 69.2, 72.4, 76.9, 77.2, 77.5, 105,7, 119.2, 126.2, 126.4, 127.3, 129.0, 133.9, 135.7, 157.9, 174.8; MS(ESI) *m/z* 319.3 (M+1).

Compound 23 (Scheme 2). Compound **23** was prepared as described above for the preparation of compound **18,** this time employing compound **15** and TsCl. Compound **23** was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give the compound as a pale yellow oil with a 93% yield. The ^{1}H NMR ($CDCl_3$) δ 1.58 (d, 3H), 2.41 (s, 3H), 3.43 (m, 2H), 3.48(m, 2H), 3.84 (q, 1H), 3.86 (s, 3H), 3.94 (t, 2H), 4.10 (m, 2H), 7.10-7.13 (m, 2H), 7.29 (d, 2H), 7.39 (d, 1H), 7.65-7.75 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.6, 21.8, 45.5, 55.5, 63.9, 68.7, 69.27, 69.27, 105.8, 119.2, 126.2, 126.4, 127.4, 128.1, 129.0, 129.4, 129.9, 133.9, 145.0, 157.9, 174.7; MS (ESI) *m/z* 473.4 (M+1).

Example 7

Compound 16 (Scheme 2). Compound **16** was prepared as described above for the preparation of compound **10,** this time employing naproxen (**1**) and 1,3-pentanediol (**8**). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound **15** with a 32% yield. The compound was used to make compound **24** without further purification; ^{1}H NMR, ^{13}C

NMR and MS are consistent with the structure of compound **16**.

Compound 24 (Scheme 2). Compound **24** was prepared as described above for the preparation of compound **18,** this time employing compound **16** and TsCl. The compound **24** was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give the compound as a pale yellow oil with a 82% yield. The ^{1}H NMR, ^{13}C NMR and MS are consistent with the structure of compound **24.**

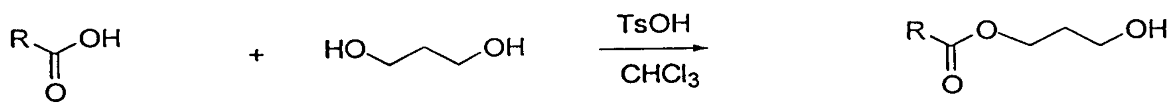
Example 8

Compound 17 (Scheme 2). Compound **17** was prepared as described above for the preparation of compound **10,** this time employing naproxen **(1)** and 1,4-cyclohexanediol **(8)**. After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound **17**. Compound **17** was used to make compound **25** without further purification; ^{1}H NMR ($CDCl_3$) δ 1.30-1.45 (m, 6H), 1.56 (d, 3H), 1.80-1.98 (m, 4H), 3.66 (m, 1H), 3.82 (q, 1H), 3.91 (s, 3H), 4.75 (m, 1H), 7.11 m, 2H), 7.39 (d, 1H), 7.65-7.70 (m, 3H); ^{13}C NMR ($CDCl_3$) 18.7, 28.2, 28.5, 32.1, 32.2, 45.9, 55.5, 68.9, 72.0, 76.9, 77.2, 77.5, 105.8, 119.1, 126.0, 126.4, 127.2, 129.1, 129.5, 133.8, 136.1, 157.8, 174.4; MS (ESI) *m/z* 351.4 (M + Na).

Compound 25 (Scheme 2). Compound **25** was prepared as described above for the preparation of compound **18,** this time employing compound **17** and TsCl. Compound **25** was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give the compound as a pale yellow oil with a 93% yield; ^{1}H NMR ($CDCl_3$) δ 1.50-1.84 (m, 11H), 2.43 (s, 3H), 3.80 (q, 1H), 3.92 (s, 3H), 4.51 (m, 1H), 4.78 (m, 1H), 7.10-7.15 (m 2H), 7.26-7.39 (m, 3H), 7.61-7.75 (m, 5H); MS (ESI) *m/z* 483.5 (M+H).

The syntheses described in Examples 9-14 are outlined in Scheme 3.

Scheme 3

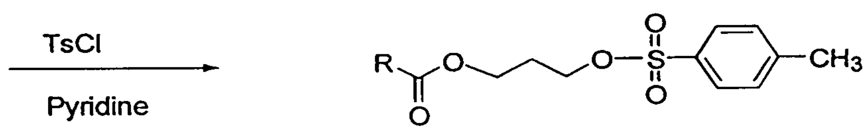


26, R = Ketoprofen
27, R = Flurbiprofen
28, R = Ibuprofen
29, R = Diclofenac
30, R = Carprofen
31, R = Indomethacin

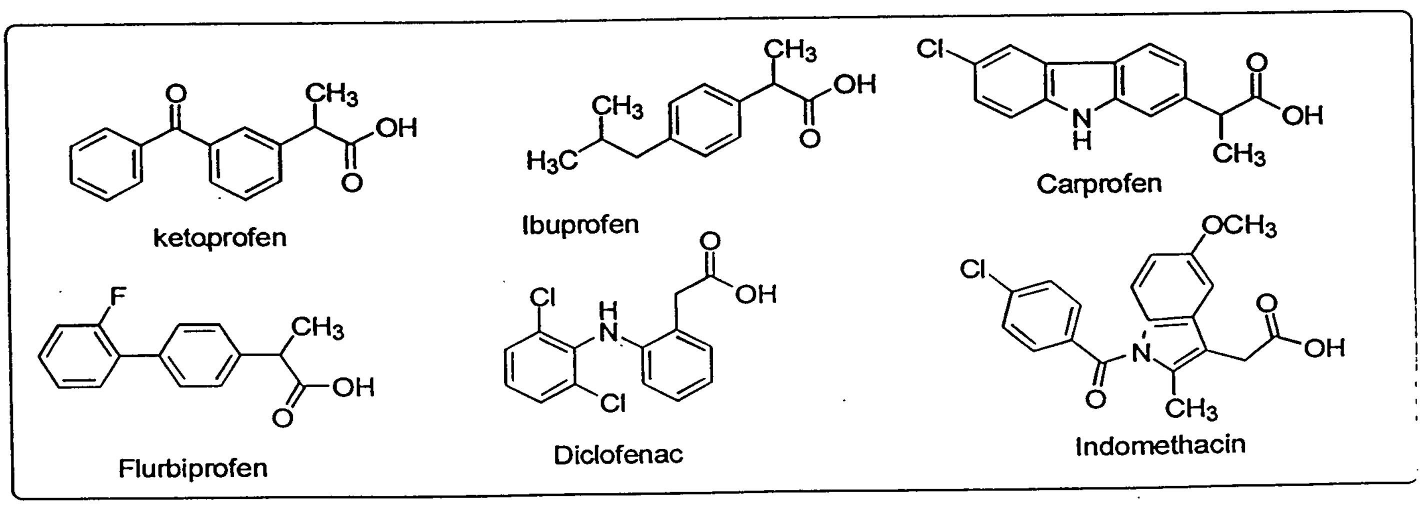
3

32, R = Ketoprofen
33, R = Flurbiprofen
34, R = Ibuprofen
35, R = Diclofenac
36, R = Carprofen
37, R = Indomethacin

T0230



38, R = Ketoprofen
39, R = Flurbiprofen
40, R = Ibuprofen
41, R = Diclofenac
42, R = Carprofen
43, R = Indomethacin



Example 9

Compound 32 (Scheme 3). Compound **32** was prepared as described above for the preparation of compound **10,** this time employing ketoprofen (**26**) and 1,3-propanediol (**3**). Compound **32** was purified by column chromatography on a silica gel column using 200:1 CH_2Cl_2/MeOH as an eluent to give compound **32** with a 50% yield. ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 3H), 1.82 (m 3H, 1H, D_2O ex), 3.58 (m, 2H), 3.82(m, 1H), 4.25 (m 2H), 7.44-7.82 (m, 9H); MS (ESI) *m/z* 313.5 (M+H).

Compound 38 (Scheme 3). Compound **38** was prepared as described above for the preparation of compound **18,** this time employing compound **32** and TsCl. Compound **38** was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give the compound **38** as a colorless oil with a 81% yield; ^{1}H NMR ($CDCl_3$) δ 1.49 (d, 3H), 1.94 (m, 2H), 2.43 (s, 3H), 3.72 (q, 1H), 4.01 (t, 2H), 4.12 (m, 2H), 7.31-7.78 (m, 13H); MS (ESI) *m/z* 467.3 (M+H).

Example 10

Compound 33 (Scheme 3). Compound **33** was prepared as described above for the preparation of compound **10,** this time employing flurbiprofen (**27**) and 1,3-propanediol (**3**). After reaction, the reaction solution was washed in water and the reaction solvent was then evaporated to give the compound **33** with a quantitative yield. The compound **33** was used to make compound **39** without further purification; ^{1}H NMR ($CDCl_3$) δ 1.54 (d, 3H), 1.79 (t, 1H, D_2O ex), 1.85 (m, 2H), 3.63 (m, 2H), 3.76 (q, 1H), 4.27 (t, 2H), 7.11-7.16(m, 2H), 7.35-7.46 (m, 4H), 7.54 (d, 2H); MS (ESI) *m/z* 325.4 (M+Na).

Compound 39 (Scheme 3). Compound **39** was prepared as described above for the preparation of compound **18,** this time employing compound **33** and TsCl. Compound **39** was purified by crystallization from ether/hexane system with a 79% yield; ^{1}H NMR ($CDCl_3$) δ 1.50 (d, 3H), 1.96 (m, 2H), 2.42 (s, 3H), 3.68 (q, 1H), 4.03 (t, 2H), 4.15 (t, 2H), 7.05-7.11 (m, 2H), 7.25-7.54 (m, 8H), 7.76 (d, 2H); ^{13}C NMR

($CDCl_3$) δ 18.4, 21.8, 28.4, 45.0, 50.8, 66.9, 115.2, 115.5, 123.68, 123.7, 127.9, 128.0, 129.2, 130.1, 131.0, 133.1, 135.6, 141.75, 141.8, 145.1, 158.9, 160.9, 173.9; MS (ESI) *m/z* 479.4 (M+Na).

Example 11

Compound 34 (Scheme 3). Compound **34** was prepared as described above for the preparation of compound **10,** this time employing ibuprofen (**28**) and 1,3-propanediol (**3**). After reaction, the reaction solution was washed in water and the reaction solvent was then evaporated to give compound **34** with a quantitative yield. The compound **34** was used to make compound **40** without further purification; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 6H), 1.49 (d, 3H), 1.79 (t, 2H), 1.78-1.85 (m, 1H), 1.95 (t, 1H, D_2O ex), 2.45 (d, 2H), 3.53 (m, 2H), 3.71 (q, 1H), 4.22 (m, 2H), 7.09 (d, 2H), 7.26 (d, 2H).

Compound 40 (Scheme 3). Compound **40** was prepared as described above for the preparation of compound **18,** this time employing compound **34** and TsCl. Compound **40** was purified by crystallization from ether/hexane system to give a white solid with a 96% yield; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 6H), 1.44 (d, 3H), 1.81-1.92 (m, 3H), 2.44 (s, 3H), 3.61 (q, 1H), 3.99 (t, 2H), 4.09 (t, 2H), 7.08 (d, 2H), 7.14 (d, 2H), 7.34 (d, 2H), 7.78 (d, 2H); ^{13}C NMR ($CDCl_3$) d 18.46, 21.80, 22.54, 28.39, 30.32, 45.16, 60.39, 66.92, 127.23, 128.04, 129.50, 130.03, 133.12, 137.68, 140.76, 145.00, 174.54; MS (ESI) *m/z* 441.5 (M + Na).

Example 12

Compound 35 (Scheme 3). Compound **35** was prepared as described above for the preparation of compound **10,** this time employing diclofenac (**29**) and 1,3-propanediol (**3**). After reaction, compound **35** was purified by column chromatography on a silica gel column using 200:1 CH_2Cl_2/MeOH as an eluent to give the compound **35** as a white solid with a 56% yield. ^{1}H NMR ($CDCl_3$) δ 1.89 (m, 3H, 1H D_2O ex), 3.66 (t, 2H), 3.83 (s, 3H), 4.31 (t, 2H), 6.55 (d, 1H), 6.87 (br, 1H), 6.94-7.00 (m, 2H), 7.11-7.14 (m, 1H), 7.22-7.26 (m, 1H), 7.34 (d, 2H); MS (ESI) *m/z*

376.3 (M+Na).

Compound 41 (Scheme 3). Compound **41** was prepared as described above for the preparation of compound **18,** this time employing compound **35** and TsCl. Compound **41** was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give the compound **41** as a pale yellow oil and the yield was 89% ; ^{1}H NMR ($CDCl_3$) δ 2.02 (m, 2H), 2.43 (s, 3H), 3.73 (s, 2H), 4.09 (t, 2H), 4.17 (t, 2H), 6.53 (d, 1H), 6.99 (s, 1H), 6.93-7.00 (m, 2H), 7.12 (t, 1H), 7.18 (d, 1H), 7.23 (d, 1H), 7.31-7.35 (m, 3H), 7.78 (d, 2H); MS (ESI) *m/z* 508.3 (M).

Example 13

Compound 36 (Scheme 3). Compound **36** was prepared as described above for the preparation of compound **10,** this time employing carprofen **(30)** and 1,3-propanediol **(3)**. After reaction, compound **36** was purified by column chromatography on a silica gel column using 200:1 CH_2Cl_2/MeOH as an eluent to give the compound **36** as a colorless oil with a 54% yield. ^{1}H NMR ($CDCl_3$) δ 1.59 (d, 3H), 1.74 (br, 1H, D_2O ex), 1.80 (m, 2H), 3.53-3.56 (m, 2H), 3.88 (q, 1H), 4.22-4.28 (m, 2H), 7.17 (d, 1H), 7.29-7.35 (m, 3H), 7.94-7.98 (m, 2H), 8.14 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 18.99, 31.84, 46.17, 59.42, 62.10, 109.70, 111.79, 119.79, 120.21, 120.87, 121.92, 124.49, 125.22, 126.09, 138.24, 139.37, 140.55, 175.39; MS (ESI) *m/z* 332.2 (M+H).

Compound 42 (Scheme 3). Compound **42** was prepared as described above for the preparation of compound **18,** this time employing compound **36** and TsCl. Compound **42** was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give the compound **42** as a sticky oil and the yield was 90% ; The ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 3H), 1.91 (m, 2H), 2.39 (s, 3H), 3.83 (q, 1H), 3.97 (t, 2H), 4.09-4.18 (m, 2H), 7.10 (d, 1H), 7.21(d, 2H), 7.32 (s, 2H), 7.38 (s, 1H)7.65 (d, 2H), 7.91 (d, 1H), 7.98 (s, 1H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.83, 21.77, 28.32, 46.08, 60.59, 57.04, 109.97, 111.97, 119.58, 120.06, 120.69, 121.77, 124.38, 125.00, 125.99, 127.95, 129.22, 130.06, 132.90, 138.38, 139.19, 140.69, 145.15, 174.59; MS

(ESI) *m/z* 486.3 (M +H).

Example 14

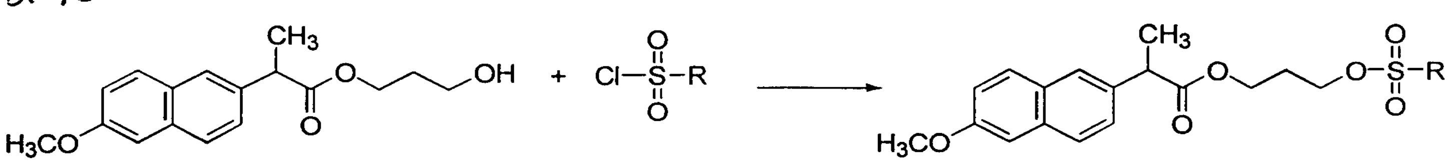
Compound 37 (Scheme 3). Compound **37** was prepared as described above for the preparation of compound **10,** this time employing indomethacin (**31**) and 1,3-propanediol (**3**). After reaction, compound **37** was purified by column chromatography on a silica gel column using 200:1; 100:1 CH_2Cl_2/MeOH as an eluents to give the compound **37** as a pale yellow oil with a 49% yield. ^{1}H NMR, ^{13}C NMR and MS are consistent with the structure of compound **37**.

Compound 43 (Scheme 3). Compound **43** was prepared as described above for the preparation of compound **18,** this time employing compound **37** and TsCl. The compound **43** was purified by column chromatography on a silica gel column using hexane/ethyl acetate (3:1) as an eluent to give the compound **43** as a pale yellow oil and the yield was 71% ; ^{1}H NMR ($CDCl_3$) δ 1.97 (m, 2H), 2.36 (s, 3H), 2.44 (s, 3H), 3.63 (s, 2H), 3.83 (s, 3H), 4.05 (t, 2H), 4.15 (t, 2H), 6.66-6.68 (m, 1H), 6.87 (d, 1H), 6.93 (d, 1H), 7.33 (d, 2H), 7.47 (d, 2H), 7.67 (d, 2H), 7.75 (d, 2H); MS (ESI) *m/z* 592.0 (M + Na).

The syntheses described in Examples 15 and 16 are outlined in Scheme 4.

Scheme 4

T0270



11

44, R = CH_3
45, R = CF_3

46, R = CH_3
47, R = CF_3

Example 15

Compound 46 (Scheme 4). Compound **46** was prepared as described above for the preparation of compound **18,** this time employing compound **11** and **44**. The compound **46** was purified by crystallization from ether/hexane system to give the compound **46** as a white solid . The yield was 95%; ^{1}H NMR ($CDCl_3$) δ 1.58 (d, 3H), 2.00 (m, 2H), 2.73 (s, 3H), 3.87 (q, 1H), 3.90 (s, 3H), 4.10 (t, 2H), 4.18 (t, 2H), 7.10-7.15 (m, 2H), 7.39 (d, 1H), 7.66-7.71 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 18.46, 28.55, 37.03, 45.56, 55.47, 55.50, 60.38, 66.36, 105.75, 119.32, 126.09, 126.27, 127.44, 129.06, 129.41, 133.89, 135.68, 157.91, 174.59; MS (ESI) *m/z* 388.5 (M + Na).

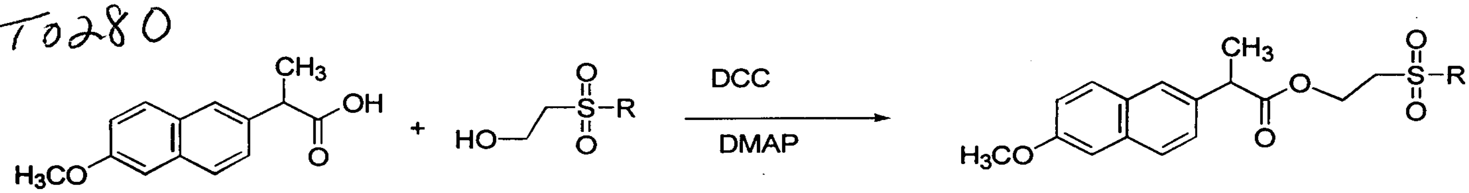
Example 16

Compound 47 (Scheme 4). Compound **47** is prepared as described above for the preparation of compound **18,** this time employing compound **11** and compound **45**. The compound is purified by crystallization and the yield was 70-90%. The ^{1}H NMR, ^{13}C NMR and MS are consistent with the structure of compound **47**.

The syntheses described in Examples 17 and 18 are outlined in Scheme 5.

Scheme 5

T0280



1

48, R = CH_3
49, R = *m*-$C_6H_4NO_2$

50, R = CH_3
51, R = *m*-$C_6H_4NO_2$

28

Example 17

Compound 50 (Scheme 5). To a solution of naproxen (**1**) (1.15g, 5 mmol), compound **48** (0.62g, 5 mmol) and dimethylamino pyridine (DMAP) (0.12g, 1 mmol) was added dicyclohexyldicarbodiimide (DCC) (1.03g, 5 mmol) at 0° C. The resulting solution was stirred at 0° C for 1.5 h. After reaction, the solid was filtered off and the solvent was evaporated. The residue was washed with ether to give 1.4g (83%) of compound **50** as a white solid; ^{1}HNMR ($CDCl_3$) δ 1.59 (d, 3H), 2.38 (s, 3H), 3.17 (m, 2H), 3.87 (q, 1H), 3.92 (s, 3H), 4.43 (m, 1H), 4.59 (m, 1H), 7.10 (d, 1H), 7.15 (m, 1H), 7.33 (m, 1H), 7.67 (d, 1H), 7.70 (m, 2H); MS (ES) *m/e* 358.2 (M+Na).

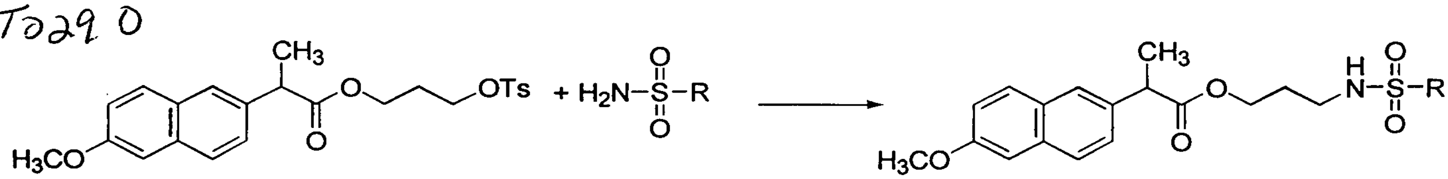
Example 18

Compound 51 (Scheme 5). Compound **51** was prepared as described above for the preparation of compound **50,** this time employing compound **1** (1.15g, 5mmol) and **49** (1.16g, 5 mmol). The compound was purified by column chromatography on a silica gel column using 1:1 hexanes/ethyl acetate as eluent to give 0.91g of compound **51** as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.45 (d, 3H), 3.48 (m, 2H), 3.59 (q, 1H), 3.92 (s, 3H), 4.47 (m, 2H), 7.10 (d, 1H), 7.18 (m, 2H), 7.45 (s, 1H), 7.49 (t, 1H), 7.65 (t, 2H), 8.06 (q, 1H), 8.28 (q, 1H), 8.68 (s, 1H); ^{13}C NMR ($CDCl_3$) 18.8, 45.2, 55.4, 55.5, 57.9, 105,8, 123.6, 125.9, 127.5, 128.4, 129.0, 129.3, 130.8, 133.7, 133.9, 134.9, 141.5, 148.4, 158.0, 174.0.

The syntheses described in Examples 19-21 are outlined in Scheme 6.

Scheme 6

T0290



19

52, R = CH_3
53, R = p-C_6H_4Me
54, R = o- $C_6H_4NO_2$

55, R = CH_3
56, R = p-C_6H_4Me
57, R = o- $C_6H_4NO_2$

Example 19

Compound 55 (Scheme 6). A mixture of compound **19** (2.2g, 5 mmol), compound **52** (0.57g, 6mmol) and K_2CO_3 (3.45g, 25 mmol) in 50 ml of dimethyl formamide (DMF) was stirred for a week. The reaction solution was poured into 100 ml of water and extracted with CH_2Cl_2. The organic phase was washed with water (50 x 5) and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography on a silica gel column using 3:1 hexane/ ethyacetate as an eluent to give 0.3g (16%) of compound **55** as a pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.60 (d, 3H), 2.38 (s, 3H), 3.17 (m, 2H), 3.87 (q, 1H), 3.92 (s, 3H), 4.45 (m, 1H), 4.59 (m, 1H), 7.10 (s, 1H), 7.14-7.16 (q, 1H), 7.32-7.35 (q, 1H), 7.62 (s, 1H), 7.67-7.71 (m, 2H); MS (ESI) *m/z* 358.2 (M + Na).

Example 20

Compound 56 (Scheme 6). Compound **56** was prepared as described above for the preparation of compound **55,** this time employing compound **19** and compound **53**. The compound was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give compound **56** as a pale yellow oil (33%). ^1HNMR ($CDCl_3$) δ 1.54 (d, 3H), 1.72 (m, 2H), 2.83 (m, 2H), 3.80 (q, 1H), 3.92 (s, 3H), 4.10 (t, 2H)7.07-8,10 (m, 10H); MS (ESI) *m/z* 442.3 (M + H).

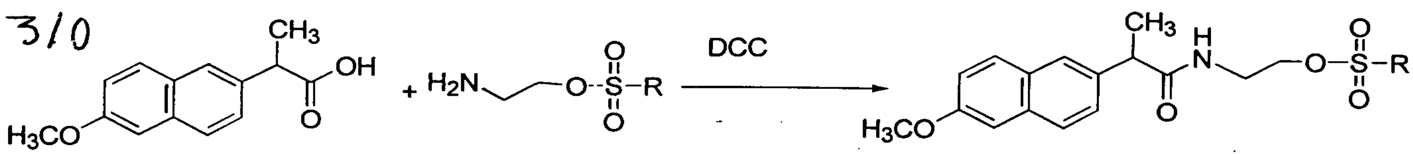
Example 21

Compound 57 (Scheme 6). Compound **57** was prepared as described above for the preparation of compound **55,** this time employing compound **19** and compound **54**. The compound was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give compound **57** as a pale yellow oil (11%). The ^1HNMR ($CDCl_3$) δ 1.55 (d, 3H), 1.80 (m, 2H), 3.03 (m 2H),3.86 (m, 1H), 4.13 (m, 2H), 7.07-7.93 (m, 10H); MS (ESI) *m/z* 473.4 (M + H).

The syntheses described in Examples 22 and 23 are outlined in Scheme 7.

Scheme 7

T0310



1

58, R = CH_3
59, R = p-C_6H_4Me

60, R = CH_3
61, R = p-C_6H_4Me

Example 22

Compound 60 (Scheme 7). Compound **60** is prepared as described above for the preparation of compound **50**, this time employing naproxen **1** and compound **58**. After reaction the compound is purified by column chromatography on a silica gel column to give the compound **60** in a yield from 75 –95%.

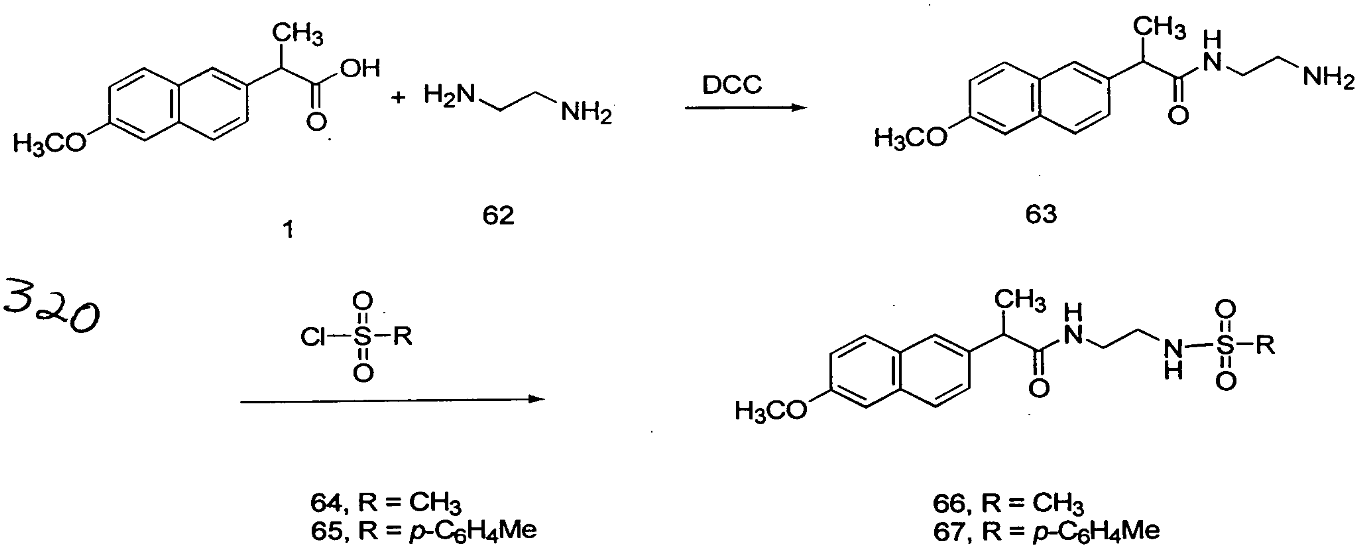
Example 23

Compound 61 (Scheme 7). Compound **61** is prepared as described above for the preparation of compound **50**, this time employing naproxen (**1**)and compound **59**. After reaction, the compound is purified by column chromatography on a silica gel column to give compound **61** in a yield from 75 –95%.

The syntheses described in Examples 24 and 25 are outlined in Scheme 8.

Scheme 8

To 320



Example 24

Compound 63 (Scheme 8). Compound **63** is prepared as described above for the preparation of compound **50,** this time employing naproxen (**1**) and compound **62**. After reaction, the compound is purified by column chromatography on a silica gel column to give compound **63** in a yield of 75 –95%.

Compound 66 (Scheme 8). Compound **66** is prepared as described above for the preparation of compound **18,** this time employing compound **63** and compound **64**.

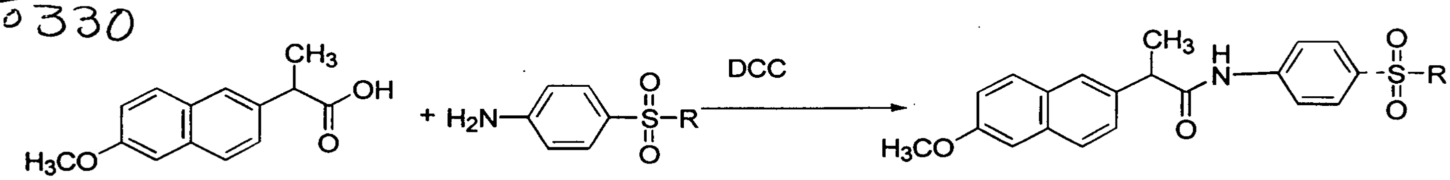
Example 25

Compound 67 (Scheme 8). Compound **67** is prepared as described above for the preparation of compound **18,** this time employing compound **63** and compound **65**.

The syntheses described in Examples 26 and 27 are outlined in Scheme 9.

Scheme 9

To 330



1

68, R = CH_3
69, R = NH_2

70, R = CH_3
71, R = NH_2

Example 26

Compound 70 (Scheme 9). Compound **70** is prepared as described above for the preparation of compound **60,** this time employing compound **1** and compound **68.**

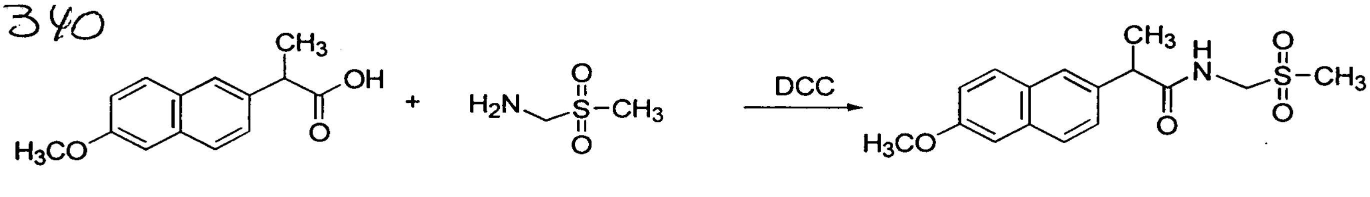
Example 27

Compound 71 (Scheme 9). Compound **71** is prepared as described above for the preparation of compound **60,** this time employing compound **1** and compound **69.**

The synthesis described in Example 28 is outlined in Scheme 10.

Scheme 10

T0340



1 72 73

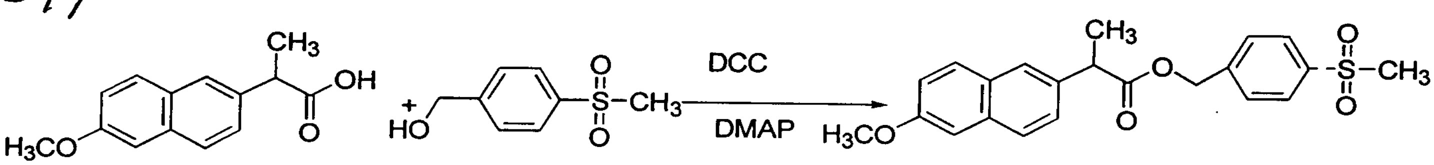
Example 28

Compound 73 (Scheme 10). Compound **73** is prepared as described above for the preparation of compound **60,** this time employing compound **1** and compound **72.**

The synthesis described in Example 29 is outlined in Scheme 11.

Scheme 11

T0341



1 74 75

Example 29

Compound 75 (Scheme 11). Compound **75** is prepared as described above for the preparation of compound **60,** this time employing compound **1** and compound **74.**

Example 30

Reduced numbers of intestinal ulcers in rat acute and subacute enteropathy models by the invention modified NSAID (compound 19), a prodrug of naproxen

NSAIDs are important drugs used to treat acute and chronic inflammation as well as pain and fever. The major limitation to NSAID use is the occurrence of gastrointestinal ulcers and erosions. These side effects are produced by a combination of local and systemic effects. Attempts have been made to circumvent the local side effects of NSAIDs by making them as prodrugs, which will bypass the stomach, but so far this has not been clearly successful. It is demonstrated here that the invention modified NSAIDs substantially reduce GI toxicity, while exhibiting dose equivalent efficacy in anti-inflammation activity in both acute and chronic inflammation animal models.

Sprague-Dawley rats (male, 150 - 200 g), were orally dosed once daily for either 3 days (acute model) or 14 days (subacute model). Twenty-four hours after the last dose, the rats were injected i.v. with Evans Blue (5 ml/kg, 10 mg/ml) to stain the ulcers. Ten to twenty minutes later the animals were sacrificed by CO_2 inhalation and the intestines removed, opened lengthwise and the contents removed. The long dimensions of all ulcers were measured using a ruler and summed to give a total ulcer score.

In the acute model (Figure 1), ulceration after dosing with an invention modified NSAID (compound 19) was 15% of that seen with an equimolar dose of naproxen. PEG had no ulcerogenic effect. In the subacute model (Figure 2), ulceration was less than 5% of that seen with a corresponding dose of naproxen at all three doses used. Again, PEG had no effect. These results suggest that invention modified NSAIDs are much less ulcerogenic than naproxen.

Example 31

Reduction of chronic hindlimb inflammation in the rat adjuvant arthritis model by the invention modified NSAID (compound 19), a prodrug of naproxen

NSAIDs are useful in the treatment of both chronic and acute inflammatory conditions. Efficacy in chronic inflammation can be estimated using the rat adjuvant arthritis model. In this model Lewis male rats (175-250 g) are injected intradermally in the footpad with M. tuberculosis powder suspended in mineral oil at 5 mg/ml. Progressive swelling of the uninjected paw and ankle joint between days 5 and 15 is measured by plethysmometry.

Rats were dosed daily by oral gavage with 5 ml/kg of naproxen at 3 to 30 mg/kg in phosplate buffered saline (PBS) and with equimolar doses of an invention modified NSAID at 1 ml/kg in PEG 300. The results (Figure 3) show that the invention modified NSAID resulted in antiinflammatory effects comparable to those of naproxen in this model.

Example 32

Reduction of acute hindlimb inflammation in the rat carrageenan-induced hindlimb edema model by the invention modified NSAID (compound 19), a prodrug of naproxen

Efficacy of NSAIDs in acute inflammation can be estimated by using intraplantar injection of carrageenan in the rat. Sprague-Dawley rats (200-250 g male) are injected intradermally in the footpad with 50 μl of a 1% carrageenan solution in PBS. Swelling of the injected paw is measured 3 & 4 hours later, using a plethysmometer.

Pretreatment with oral naproxen one hour before the carrageenan injection at 10 mg/kg resulted in an approximately 50% reduction in swelling at both time points (Table 1). An equimolar dose of an invention modified NSAID reduced inflammation to the same degree at both time points. These results suggest that invention modified NSAIDs are comparable in effect to naproxen at 10 mg/kg.

To 370

Table 1. Effects of naproxen and the invention modified NSAID (compound 19) on paw volume increase in carrageenan-induced inflammation in rats.

Treatment	4 Hours	5 Hours
Vehicle	0.73 ± 0.10	0.85 ± 0.10
Naproxen (1 mg/kg)	0.63 ± 0.07	0.75 ± 0.08
Naproxen (10 mg/kg)	0.32 ± 0.05*	0.39 ± 0.07*
Compound 19 (1.75 mg/kg)	0.78 ± 0.04	0.93 ± 0.04
Compound 19 (17.5 mg/kg)	0.34 ± 0.06*	0.40 ± 0.06*

* $P < 0.05$ vs Vehicle by unpaired t-test.

Invention modified NSAIDs are seen to have antiinflammatory activity similar to naproxen in the chronic adjuvant arthritis and acute carrageenan hindlimb edema rat models. The tendency to cause intestinal ulcers is reduced substantially inventon modified NSAID. Thus, invention modified NSAIDs provide an effective prodrug form of naproxen with reduced intestinal side effects.

Example 33

Plasma pharmacokinetics of naproxen and the invention modified NSAID after oral administration in rats

The invention compound (compound 19) is a naproxen prodrug, which is a conjugate of naproxen and tosylate. Oral administration of the invention compound resulted in the release of free naproxen. The pharmacokinetics of naproxen release from the invention modified NSAID and its parent drug, naproxen, was evaluated in rats after oral administration.

The carotid artery of Sprague-Dawley rat (250-350 g, male) was catheterized at least one day before drug administration and flushed with 30% polyvinyl pyrrolidone (PVP) (400 U/mL of heparin) to maintain patency. At predetermined time points (see Table 2), blood samples (250 μL) were collected by unhooking the flushing syringe and letting the blood flow out of the catheter and into the centrifuge

tubes. After centrifugation (13,000 rpm, 10 min, 4°C), the plasma samples were collected and analyzed in the same day.

To380

Table 2: Rat group assignment and doses

Test Article	Group #	Rat #	Dose* (mg/kg)	Sample Time
Naproxen	1	1, 2, 3, & 4	Oral (2 mg/kg)	5 min, 0.5, 1, 4, 7, 10, 13, 16, 19, 22, & 24 hrs
Invention Compound 19	2	5, 6, 7, & 8	Oral (2 mg/kg)	15 min, 0.5, 1, 3, 5, 6, 7, 8, 22, 23, & 24 hrs

*Indicates amount of naproxen in dose.

Aliquot of plasma sample (100 µL) was mixed with 200 µL of acetonitrile. After vortexing and centrifugation (13,000 rpm, 10 min, 4°C), 200 µL of supernatant was removed and added to 300 µL of a 58:42 mixture of 50 mM phosphate buffer (pH 5.0) and acetonitrile. Following vortexing and centrifugation, 25 µL of supernatant was removed and analyzed by HPLC with a UV detection system.

The average plasma concentration at each time point was calculated and utilized in a pharmacokinetic analysis. Noncompartmental pharmacokinetic analysis was carried out using WinNolin (Pharsight, Mountainview, California) to calculate the maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve from zero to the last time point (AUC_{last}), the area under the curve from zero to infinite time (AUC_{inf}), and the terminal phase half life (Beta-$t_{1/2}$).

The AUC_{all}, AUC_{INF}, and $t_{1/2}$ of naproxen from naproxen and a modified form of naproxen according to the invention were found to be similar (Table 3). On the other hand, for the invention modified form of neproxen, the C_{max} was lower and the T_{max} longer, compared to naproxen (see Table 3).

Table 3 - Non-Compartmental Pharmacokinetic Analysis of naproxen and the invention modified form of naproxen according to the (compound 19) after oral administration in rats

Drug	Dose*	C_{max}	T_{max}	AUC_{all}	AUC_{INF}	$t_{1/2}$	N
	(mg/kg)	(µg/mL)	(hrs)	(µg*hr/mL)		(hrs)	
Naproxen	2	7.77±4.13	0.5±0.5	50±6	55±7	6.2±0.4	4
Invention modified naproxen	2	3.87±1.05	6.8±1.5	49±10	56±14	6.8±2.7	4

To 390

*Indicates amount of naproxen in dose.

Following oral naproxen administration, the naproxen plasma levels were at the highest at the first time-point (5 minutes) then declined in a bi-exponential manner. In contrast, after oral administration of a modified form of naproxen according to the invention, the maximum naproxen levels were observed at a much later time (T_{max} of 6.8±1.5 hrs). The similar AUC_{all}, AUC_{INF}, and $T_{1/2}$ values but lower C_{max} and longer T_{max} values supports the conclusions drawn from the results obtained from pharmacological studies, i.e. that a modified form of naproxen according to the invention conjugate has equivalent pharmacological efficacy and greatly improved gastrointestinal safety profile compared to naproxen.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.